Hypereosinophilia

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Eosinophils

- First described in 1879 by Dr. Ehrlich
- Stained with acidic dyes, eosin
- Recognized early that they are associated with helminthic infections, asthma, malignancy
- Differentiate from hematopoietic stem cells
- Blood half-life of 18 hrs

Eosinophils

- Mainly tissue dwellers with 100 tissue eo’s per 1 blood eosinophil
- Tissue half-life of 7-14 days
- Blood eosinophil count is a reflection of a balance between marrow production, tissue migration, and death by apoptosis
- Increase in numbers depends on T cells
- Cytokines: IL-2, IL-3, IL-5, GM-CSF

Eosinophils

- Arbitrary definitions:
  - Normal= up to 350 cells/cc
  - Mild= 351-1500
  - Moderate= 1501-5000
  - Severe= >5000 cells/cc
- Most common cause worldwide is helminthic infection
- Industrial nations= atopic disease

Differential based on eos level

Table 2 Causes of mild, moderate and severe eosinophilia

Mild	Allergic rhinitis, atopic dermatitis, asthma, urticaria/skin diseases, bronchiectasis, cystic fibrosis, Langerhans cell histiocytosis
Mild to moderate	Eosinophilic gastroenteritis, non-haematological malignancy
Moderate	Lymphomas, bullous pemphigoid, rheumatoid arthritis, drug reactions, IL2 therapy
Moderate to severe	Churg–Strauss, rheumatoid arthritis, connective tissue diseases, pulmonary eosinophilia, clonal eosinophilia, idiopathic HES, parasitic infestations/VLM/TPE, eosinophilic fasciitis, toxic oil syndrome, endomyocardial fibrosis

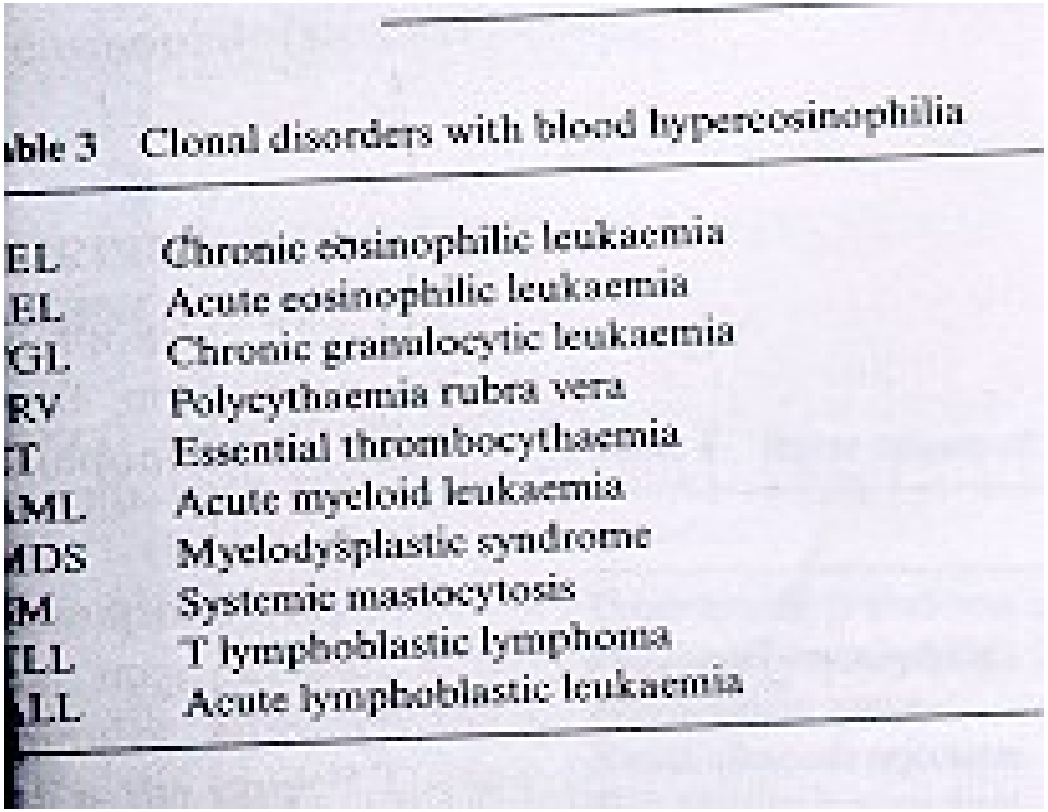
Clonal v. Reactive

- Difficult to distinguish
- Clonal disorders include: CEL, AEL, PRV, ET, AML, MDS, TLL, ALL
- Some clues: cytogenetics, FISH, G6PD alloenzyme, ALIP, myelodysplasia, T-cell gene rearrangement
- Other support: elevated B12 binding, poor response to steroids, low LAP, organomegal

Clonal v. Reactive

- Cytokine levels can be normal in clonal disorders
- Severe and progressive eosinophilia more likely to be clonal
- End organ damage can be caused by clonal and reactive disorders

Clonal disorders



ble 3 Clonal disorders with blood hypereosinophilia

EL	Chronic eosinophilic leukaemia
EL	Acute eosinophilic leukaemia
GL	Chronic granulocytic leukaemia
RV	Polycythaemia rubra vera
T	Essential thrombocythaemia
ML	Acute myeloid leukaemia
DS	Myelodysplastic syndrome
M	Systemic mastocytosis
LL	T lymphoblastic lymphoma
LL	Acute lymphoblastic leukaemia

CEL

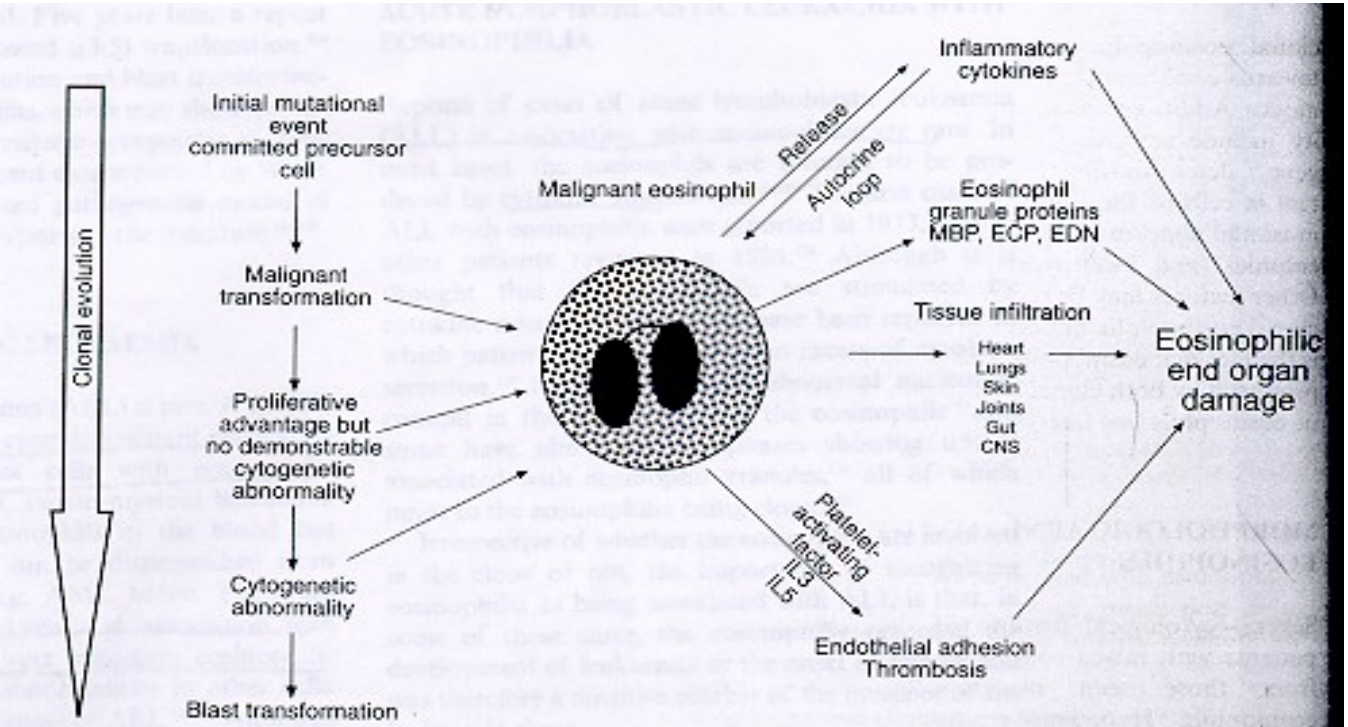


Fig. 2 Diagrammatic pathogenetic model of chronic eosinophilic leukaemia. *Abbreviations*: MBP,-major basic protein; ECP, eosinophilic cationic protein; EDN, eosinophil derived neurotoxin; PAF, platelet-activating factor.

Workup for hypereosinophilia

Table 9 Management of a patient with persistent hypereosinophilia

Exclude reactive causes
Look for underlying malignancy
Perform bone marrow aspirate, trephine biopsy and cytogenetic analysis
↓
Normal marrow with normal eosinophils and precursors and normal cytogenetic result
↓
Normal neutrophil alkaline phosphatase (NAP) and B12 binding
Measure levels of interleukins and γIFN
Look for end organ damage (ECHO/ECG)
Look for RAS mutations
Look for T cell receptor gene rearrangements
Analyse clonality of cultured or IL2 stimulated eosinophils

HES by definition

Therapy

- Acute leukemia: standard induction chemotherapy
- Leukapharesis
- Corticosteroids
- Hydroxyurea
- Alpha-interferon

Drug Therapy for eosinophilia

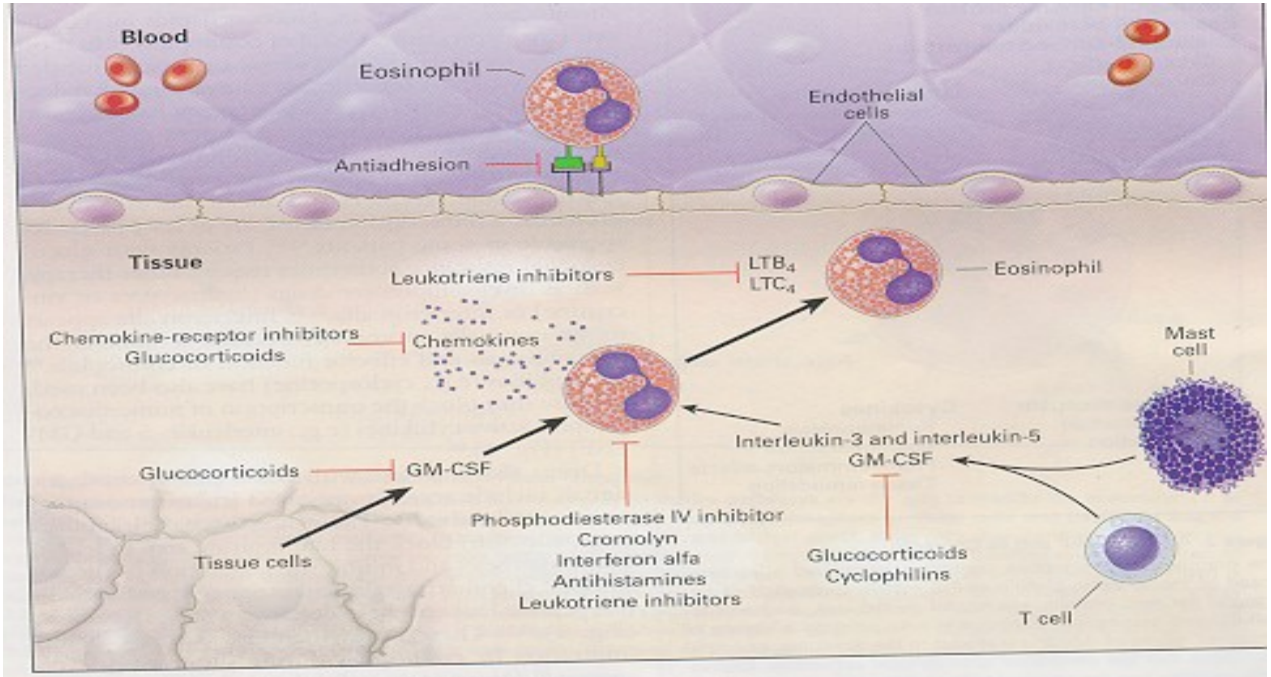


Figure 4. Approaches to Drug Therapy for Eosinophilia.
Treatment of eosinophilia involves inhibiting the interaction between eosinophils and endothelial cells through interference wi
the adhesion molecules used by these cells. Such approaches include the use of neutralizing antibodies against adhesion molecul
such as intercellular adhesion molecule 1 or very late antigen 4. The chemoattraction process can be targeted at various ste
including interference with the synthesis or activity of leukotriene B_4 (LTB_4) and leukotriene C_4 (LTC_4), chemokine-receptor inhibito
or G-protein inhibitors that block receptors for chemoattractant molecules. The proliferation, survival, and activation of eosinoph
can be blocked by interfering with the generation of eosinophil hematopoietins such as granulocyte–macrophage colony-stimul
ing factor (GM-CSF), interleukin-3, and interleukin-5 with glucocorticoids or cyclophilins (e.g., cyclosporine). Eosinophils are inh
ited by phosphodiesterase inhibitors, cromolyn, interferon alfa, antihistamines, and leukotriene inhibitors.

Specific agents

TABLE 2. PHARMACOLOGIC APPROACHES TO BLOCKING EOSINOPHILIA OR THE ACTION OF EOSINOPHILS.

DRUGS	MECHANISM OF ACTION
In use	
Primary	
Glucocorticoids	Inhibit transcription of eosinophil-directed cytokines
Interferon alfa	Inhibits degranulation and effector function of eosinophils
Myelosuppressive drugs	Suppress proliferation of eosinophils
Secondary	
Antihistamines	Inhibit degranulation and accumulation of eosinophils
Cromolyn	Inhibits effector function of eosinophils
Cyclosporine	Inhibits transcription of eosinophil-directed cytokines
Leukotriene inhibitors and antagonists	Prevent synthesis of leukotrienes or block leukotriene function
Phosphodiesterase inhibitors	Elevate intracellular cyclic AMP in eosinophils, inhibiting intracellular signaling
In development*	
Agents that block the CD18–ICAM-1 pathway	Inhibit adhesion of eosinophils
Agents that block selectins	Inhibit rolling of eosinophils
Agents that block the VLA-4–VCAM-1 pathway	Inhibit adhesion of eosinophils
Chemokine inhibitors and antagonists	Interfere with chemotaxis and activation of eosinophils
Interleukin-5 inhibitors and antagonists	Inhibit growth, survival, priming, and activation of eosinophils
Interleukin-12	Shifts Th2 immunity to Th1 immunity
Lidocaine and sulfonylurea-receptor inhibitors	Inhibit eosinophil survival
Phosphodiesterase IV inhibitors	Inhibit leukocyte-specific isoenzyme

*ICAM-1 denotes intercellular adhesion molecule 1, VLA-4 very late antigen 4, and VCAM-1 vascular-cell adhesion molecule 1.

IHES

- Criteria:
  - Sustained elevated eos count for > 6 month
  - No other apparent etiology
  - Signs of end organ damage
- Clonal disorders are excluded
- Many reported cases were likely clonal in origin

IHES

- Median survival of 9 months
- 12% three year survival
- Treatment is with corticosteroids
- Can also use steroid sparing immunosuppressive agents

IHES

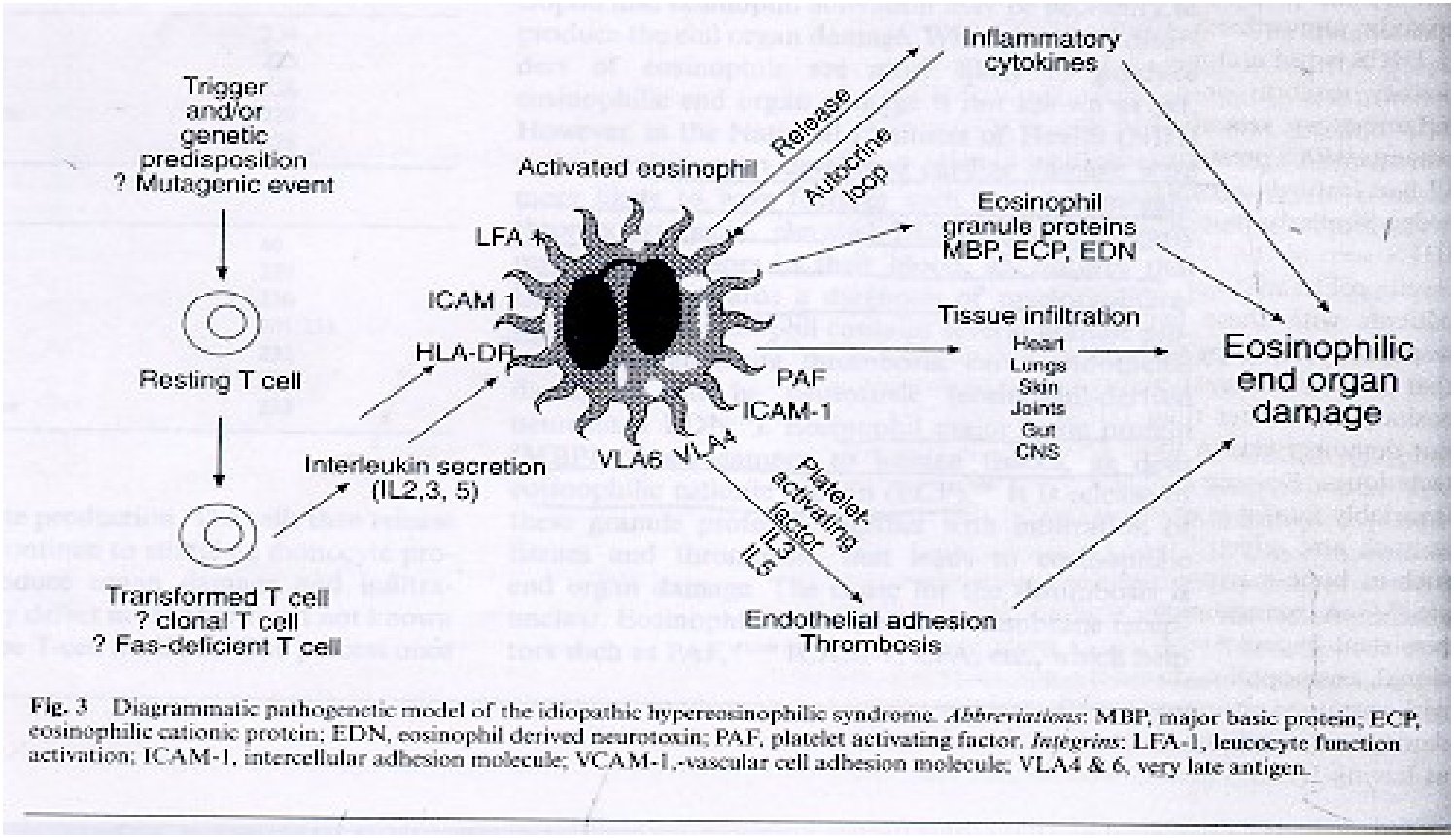


Fig. 3 Diagrammatic pathogenetic model of the idiopathic hypereosinophilic syndrome. *Abbreviations*: MBP, major basic protein; ECP, eosinophilic cationic protein; EDN, eosinophil derived neurotoxin; PAF, platelet activating factor. *Integrins*: LFA-1, leucocyte function activation; ICAM-1, intercellular adhesion molecule; VCAM-1,-vascular cell adhesion molecule; VLA4 & 6, very late antigen.

Paraneoplastic Syndrome

- Well reported in the hematologic malignancies
  - Hodgkins disease, cutaneous Tcell lymphomas
- Solid tumors have also been reported
  - epithelial based tumors: lung, ovarian, breast
  - tumors can secrete GM-CSF, IL2, IL5
- Handful of case reports with thyroid tumor